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ctDNA-based DNADX in hormone receptor-positive and HER2-negative (HR+/HER2-) advanced breast cancer following endocrine therapy and CDK4/6 inhibition: a correlative analysis from the randomized phase 2 PARSIFAL trial

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Background

- The PARSIFAL trial (NCT02491983) randomized 486 patients (pts) with endocrine-sensitive, HR+/HER2- advanced breast cancer to receive (1:1 ratio) first-line palbociclib with either fulvestrant or letrozole[1]. Both treatments had comparable efficacy and safety results (**Figure 1**).
- DNADX, a novel machine learning-based approach, utilizes DNA from tumor tissue or plasma circulating tumor DNA (ctDNA) to identify clinically relevant phenotypic tumor features and classify breast cancer into 4 subtypes[2] (**Figure 2**).
- Here, we evaluated DNADX's ability to predict prognosis and treatment benefit in endocrine-sensitive HR+/HER2- advanced breast cancer following endocrine therapy and a CDK4/6 inhibitor.

Figure 1. PARSIFAL trial design

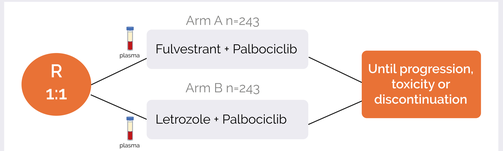
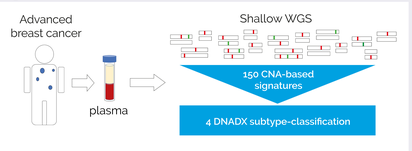


Figure 2. DNADX test



Methods

- DNADX was evaluated centrally in available baseline pre-treatment plasma samples from the PARSIFAL trial. Shallow whole genome sequencing (WGS) was performed on cell-free DNA (cfDNA), and the 4 DNA-based subtypes (Clusters-1, -2, -3, and -4) were identified if the tumor fraction (TF)≥3% (**Figure 2**).
- The main objective was to evaluate the association of DNADX subtypes with progression-free survival (PFS) and overall survival (OS).
- Secondary objective was to identify the subgroup of pts who benefit more from each endocrine treatment.
- Uni- and multi-variable Cox regression models were used after adjusting for TF, menopausal status, ECOG performance status, de novo metastasis (vs. recurrence), visceral disease, and number of metastatic sites.

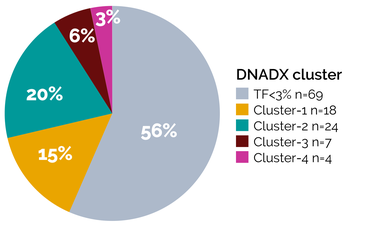
Results

- DNADX was evaluated in ctDNA samples from 122 pts (25.1%). Clinical variables were similar to overall PARSIFAL population (**Table 1**).
- DNADX cluster distribution and biology are represented in **Figures 3** and **4**.

Table 1. Patient characteristics

		All (n=122)		Palbociclib-Fulvestrant (n=62)		Palbociclib-Letrozole (n=60)	
Variable		n	%	n	%	n	%
Age		59.5 (31-84)		60 (31-84)		59 (35-83)	
Race							
	Asian	1	0.8	1	1.6	0	0
	Black	1	0.8	1	1.6	0	0
	White	120	98.4	60	96.8	60	100
ECOG performance							
	0	70	57.4	38	61.3	32	53.3
	1	77	63.1	50	80.6	27	45
	2	5	4.1	4	6.5	1	1.7
Menopausal status							
	Premenopausal	15	12.3	7	11.3	8	13.3
	Postmenopausal	107	87.7	55	88.7	52	86.7
Type of disease							
	De novo	56	45.9	27	43.5	29	48.3
	Recurrent	66	54.1	35	56.5	31	51.7
Disease site							
	Visceral	70	57.4	33	53.2	37	61.7
	Non-visceral	52	42.6	29	46.8	23	38.3
Number of disease sites							
	<3	60	49.2	34	54.8	26	43.3
	>=3	62	50.8	28	45.2	34	56.7
Mesurable disease							
	Yes	101	82.8	51	82.3	50	83.3
	No	21	17.2	11	17.7	10	16.7

Figure 3. DNADX cluster distribution



- In terms of PFS, pts classified in Cluster-2, Cluster-3, and Cluster-4 subtypes had a higher risk of progression (**Table 2 and Figure 5**).
- In terms of OS, pts classified with TF<3% had a lower risk of death compared to Cluster-2, Cluster-3, and Cluster-4 subtypes (**Table 2 and Figure 5**).
- Similar results were obtained for PFS and OS after adjusting for other clinical-pathologic variables (**Table 2**).
- The interaction test in terms of PFS suggested a benefit of fulvestrant over letrozole in Cluster-1 and Cluster-4 (**Table 3**).

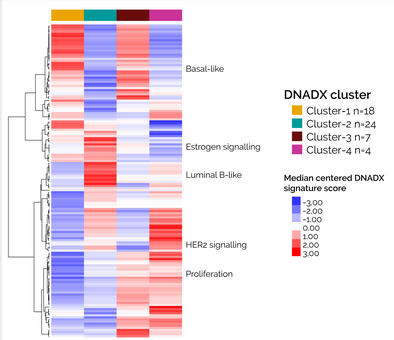
Table 2. PFS and OS by DNADX group

Model	Group	PFS HR (95% CI)	p-value	OS HR (95% CI)	p-value
Univariate	TF<3%	Ref.		Ref.	
	Cluster 1	1.88 (0.90-3.90)	0.091	1.90 (0.48-7.61)	0.363
	Cluster 2	2.02 (1.07-3.82)	0.031	4.23 (1.46-12.282)	0.008
	Cluster 3	3.15 (1.20-8.24)	0.020	11.13 (3.11-39.80)	<0.001
	Cluster 4	5.62 (1.95-16.20)	0.001	6.80 (1.36-33.95)	0.019
Multivariable*	TF<3%	Ref.		Ref.	
	Cluster 1	1.72 (0.81-3.66)	0.158	1.67 (0.40-6.92)	0.479
	Cluster 2	1.89 (0.97-3.65)	0.060	3.65 (1.18-11.28)	0.024
	Cluster 3	2.56 (0.92-7.14)	0.073	11.19 (2.66-47.02)	<0.001
	Cluster 4	4.55 (1.50-13.88)	0.007	7.22 (1.27-40.97)	0.026

Table 3. PFS benefit of fulvestrant over letrozole

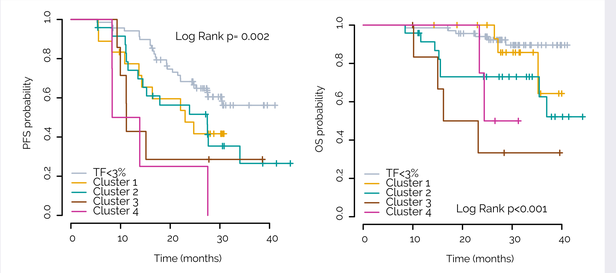
Model	Group	PFS HR (95% CI)	p-value	interaction test
Univariate	TF<3%	Ref.		
	Cluster 1	0.23 (0.05-1.04)	0.060	
	Cluster 2	0.57 (0.16-2.08)	0.390	p=0.046
	Cluster 3	2.51 (0.34-18.36)	0.360	
	Cluster 4	0.06 (0.01-0.59)	0.020	
Multivariable*	TF<3%	Ref.		
	Cluster 1	0.18 (0.04-0.87)	0.030	
	Cluster 2	0.52 (0.13-2.10)	0.360	p=0.037
	Cluster 3	1.53 (0.19-12.70)	0.690	
	Cluster 4	0.05 (0.01-0.48)	0.010	

Figure 4. DNADX cluster biology



*menopausal status, ECOG performance status, de novo metastasis (vs. recurrence), visceral disease, and number of metastatic sites.
HR: hazard ratio, CI: confidence intervals. Ref.: reference

Figure 5. PFS and OS by DNADX group



Conclusion

Liquid biopsy-based DNADX subtypes predict outcomes in pts with endocrine-sensitive HR+/HER2- advanced breast cancer on first-line endocrine therapy and CDK4/6 inhibitors, potentially identifying the most optimal endocrine treatment for each patient.

References: 1. Llombart-Cussac et al. JAMA Oncol. 2021. 2. Prat et al. Nature Commun. 2023.
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Conflicts of interest of the first author: FBM is an inventor of a filed patent related to DNADX.

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